APPENDIX II

300. A method of treating tissue to prevent or control air or fluid leaks comprising:

providing a composition to tissue, said composition including an albumin protein ***at about 20-60 wt/vol%*** and a crosslinking agent ***at about 50-800 mg/ml***, said crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein ***and having a molecular weight of about 1000-15,000***; and

curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix.

301. The method of claim ***300*** wherein said composition is cured to produce the matrix in less than about 10 minutes.

302. The method of claim ***300*** wherein said composition is cured to produce the matrix in less than about one minute.

303. The method of claim ***300*** wherein said composition is cured to produce the matrix in about ten seconds.

304. The method of claim ***300*** comprising providing the composition to the tissue using a syringe.

305. The method of claim ***300*** comprising providing the composition to the tissue using a dual syringe.

306. The method of claim ***300*** comprising providing the composition to the tissue using a spray apparatus.

307. The method of claim ***300*** wherein the matrix is resorbed.

308. The method of claim ***307*** wherein the matrix is resorbed in about four to sixty days.

309. The method of claim *300* comprising curing the composition such that the peel strength of the matrix is about 0.08 lb/in or more.

310. The method of claim *300* comprising curing said composition to provide a cured matrix that has a burst pressure greater than about 10 mmHg.

311. The method of claim *309* wherein the matrix has a burst pressure of about 34 mmHg or greater.

312. The method of claim *311* wherein the matrix has a burst pressure of about 90 mmHg or greater.

313. The method of claim *312* wherein the matrix has a burst pressure of about 130 mmHg or greater.

314. The method of claim *300* comprising providing a composition wherein the crosslinking agent has a molecular weight in a range of about 1,000-5,000.

315. The method of claim *300* comprising providing a composition wherein the activated leaving group is an N-hydroxy imide.

316. The method of claim *315* comprising providing a composition wherein the activated leaving group is N-hydroxy succinimide.

317. The method of claim *300* further comprising mixing a first mixture and a second mixture to form the composition and applying said composition to the tissue,

wherein the first mixture includes about 20-60 wt/vol% of the protein in about 0.01-0.25 molar buffer at a pH in a range of about 8.0-11.0 and the second mixture includes about 50-800 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-15,000.

318. The method of claim *317* wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula
$-O-(CH_2-CH_2-O-)_a-$
where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula, -C(O)-, a monoester diradical of the formula, $-(CH_2)_bC(O)-$ where b is an integer from 1-5, a diester radical of the formula, $-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, and a dicarbonate diradical of the formula $-C(O)-O-(CH_2)_d-O-C(O)-$ where d is an integer from 2-10, or an oligomeric diradical represented by the formulas -R-C(O)-, $-R-C(O)-(CH_2)_c-C(O)-$, or $-R-C(O)-O-(CH_2)_d-O-$ where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, or tresyl.

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319. The method of claim ***318*** wherein the protein in the first mixture is about 35-45 wt/vol% serum albumin.

320. The method of claim ***319*** wherein the buffer is 0.05-0.15 molar carbonate/bicarbonate buffer at a pH of about 9.0-10.5.

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321. The method of claim ***318*** wherein the second mixture is about 5-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

322. The method of claim ***318*** wherein the ratio of a volume of the first mixture to a volume of the second mixture is in a range of about 1:10 to about 10:1.

323. The method of claim ***318*** wherein -LM- is an oligomeric diradical $-R-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone.

324. The method of claim ***318*** wherein -G is succinimidyl.

325. The method of claim *318* wherein the second mixture includes about 300-800 mg/ml of a crosslinking agent having a molecular weight in a range of about 5,000-15,000.

326. The method of claim *318* wherein -LM- is a diester diradical of the formula $-C(O)-(CH_2)_2-C(O)-$.

327. The method of claim *318* wherein -LM- is a diester diradical of the formula $-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated.

328. The method of claim *318* wherein -LM- is an oligomeric diradical derived from polyglycolic acid.

329. The method of claim *300* comprising treating tissue to prevent or control a fluid leak.

330. The method of claim *329* wherein the fluid leak is a blood leak.

331. The method of claim *300* wherein the tissue includes an air leak.

332. The method of claim *331* wherein the air leak is in the pulmonary system.

333. A method of treating tissue to prevent formation of an adhesion comprising:

providing a composition to tissue, said composition including an albumin protein ***at about 20-60 wt/vol%*** and a crosslinking agent ***at about 50-800 mg/ml***, said crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein ***and having a molecular weight in a range of about 1000-15,000***; and

curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix.

334. The method of claim *333* wherein said composition is cured to produce the matrix in less than about 10 minutes.

335. The method of claim *333* wherein said composition is cured to produce the matrix in less than about one minute.

336. The method of claim *333* wherein said composition is cured to produce the matrix in about ten seconds.

337. The method of claim *333* comprising providing the composition to the tissue using a syringe.

338. The method of claim *333* comprising providing the composition to the tissue using a dual syringe.

B1 Cont.

339. The method of claim *333* comprising providing the composition to the tissue using a spray apparatus.

340. The method of claim *333* wherein the matrix is resorbed.

341. The method of claim *340* wherein the matrix is resorbed in about four to sixty days.

342. The method of claim *333* comprising curing the composition such that the peel strength of the matrix is about 0.08 lb/in or more.

343. The method of claim *333* comprising curing said composition to provide a cured matrix that has a burst pressure greater than about 10 mmHg.

344. The method of claim *343* wherein the matrix has a burst pressure of about 34 mmHg or greater.

345. The method of claim *344* wherein the matrix has a burst pressure of about 90 mmHg or greater.

346. The method of claim *345* wherein the matrix has a burst pressure of about 130 mmHg or greater.

347. The method of claim ***333*** comprising providing a composition wherein the crosslinking agent has a molecular weight in a range of about 1,000-5,000.

348. The method of claim ***333*** comprising providing a composition wherein the activated leaving group is an N-hydroxy imide.

349. The method of claim ***348*** comprising providing a composition wherein the activated leaving group is N-hydroxy succinimide.

350. The method of claim ***333*** further comprising mixing a first mixture and a second mixture to form the composition and applying said composition to the tissue,

wherein the first mixture includes about 20-60 wt/vol% of the protein in about 0.01-0.25 molar buffer at a pH in a range of about 8.0-11.0 and the second mixture includes about 50-800 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-15,000.

B1 Cont.

351. The method of claim ***350*** wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

$-O-(CH_2-CH_2-O-)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula, -C(O)-, a monoester diradical of the formula, $-(CH_2)_bC(O)-$ where b is an integer from 1-5, a diester radical of the formula, $-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, and a dicarbonate diradical of the formula $-C(O)-O-(CH_2)_d-O-C(O)-$ where d is an integer from 2-10, or an oligomeric diradical represented by the formulas -R-C(O)-, $-R-C(O)-(CH_2)_c-C(O)-$, or $-R-C(O)-O-(CH_2)_d-O-$ where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, or tresyl.

352. The method of claim *351* wherein the protein in the first mixture is about 35-45 wt/vol% serum albumin.

353. The method of claim *352* wherein the buffer is 0.05-0.15 molar carbonate/bicarbonate buffer at a pH of about 9.0-10.5.

354. The method of claim *351* wherein the second mixture is about 5-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

355. The method of claim *351* wherein the ratio of a volume of the first mixture to a volume of the second mixture is in a range of about 1:10 to about 10:1.

356. The method of claim *351* wherein -LM- is an oligomeric diradical -R-C(O)-$(CH_2)_c$-C(O)- where c is an integer from 2-10 and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone.

357. The method of claim *351* wherein -G is succinimidyl.

358. The method of claim *351* wherein the second mixture includes about 300-800 mg/ml of a crosslinking agent having a molecular weight in a range of about 5,000-15,000.

359. The method of claim *351* wherein -LM- is a diester diradical of the formula -C(O)-$(CH_2)_2$-C(O)-.

360. The method of claim *351* wherein -LM- is a diester diradical of the formula -C(O)-$(CH_2)_c$-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated.

361. The method of claim *351* wherein -LM- is an oligomeric diradical derived from polyglycolic acid.

362. The method of claim ***333*** wherein the composition is provided to tissue at a surgical site.

363. The method of claim ***333*** wherein the composition is provided on a surface of an internal organ.

364. A method of treating tissue to bind layers of tissue together comprising:

providing a composition to tissue, said composition including an albumin protein ***of about 20-60 wt/vol%*** and a crosslinking agent ***at about 50-800 mg/ml***, said crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein ***having a molecular weight in a range of about 1000-15,000***; and

curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix.

B1 Cont.

365. The method of claim ***364*** wherein said composition is cured to produce the matrix in less than about 10 minutes.

366. The method of claim ***364*** wherein said composition is cured to produce the matrix in less than about one minute.

367. The method of claim ***364*** wherein said composition is cured to produce the matrix in about ten seconds.

368. The method of claim ***364*** comprising providing the composition to the tissue using a syringe.

369. The method of claim ***364*** comprising providing the composition to the tissue using a dual syringe.

370. The method of claim ***364*** comprising providing the composition to the tissue using a spray apparatus.

371. The method of claim ***364*** wherein the matrix is resorbed.

372. The method of claim *371* wherein the matrix is resorbed in about four to sixty days.

373. The method of claim *364* comprising curing the composition such that the peel strength of the matrix is about 0.08 lb/in or more.

374. The method of claim *364* comprising curing said composition to provide a cured matrix that has a burst pressure greater than about 10 mmHg.

375. The method of claim *374* wherein the matrix has a burst pressure of about 34 mmHg or greater.

B1 Cont.

376. The method of claim *375* wherein the matrix has a burst pressure of about 90 mmHg or greater.

377. The method of claim *376* wherein the matrix has a burst pressure of about 130 mmHg or greater.

378. The method of claim *364* comprising providing a composition wherein the crosslinking agent has a molecular weight in a range of about 1,000-5,000.

379. The method of claim *364* comprising providing a composition wherein the activated leaving group is an N-hydroxy imide.

380. The method of claim *379* comprising providing a composition wherein the activated leaving group is N-hydroxy succinimide.

381. The method of claim *364* further comprising mixing a first mixture and a second mixture to form the composition and applying said composition to the tissue,

wherein the first mixture includes about 20-60 wt/vol% of the protein in about 0.01-0.25 molar buffer at a pH in a range of about 8.0-11.0 and the second mixture includes about 50-800 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-15,000.

382. The method of claim ***381*** wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

$-O-(CH_2-CH_2-O-)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula, -C(O)-, a monoester diradical of the formula, $-(CH_2)_bC(O)-$ where b is an integer from 1-5, a diester radical of the formula, $-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, and a dicarbonate diradical of the formula $-C(O)-O-(CH_2)_d-O-C(O)-$ where d is an integer from 2-10, or an oligomeric diradical represented by the formulas -R-C(O)-, $-R-C(O)-(CH_2)_c-C(O)-$, or $-R-C(O)-O-(CH_2)_d-O-$ where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, or tresyl.

383. The method of claim ***382*** wherein the protein in the first mixture is about 35-45 wt/vol% serum albumin.

384. The method of claim ***383*** wherein the buffer is 0.05-0.15 molar carbonate/bicarbonate buffer at a pH of about 9.0-10.5.

385. The method of claim ***382*** wherein the second mixture is about 5-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

386. The method of claim ***382*** wherein the ratio of a volume of the first mixture to a volume of the second mixture is in a range of about 1:10 to about 10:1.

387. The method of claim ***382*** wherein -LM- is an oligomeric diradical $-R-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and R is a polymer or copolymer

having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone.

388. The method of claim ***382*** wherein -G is succinimidyl.

389. The method of claim ***382*** wherein the second mixture includes about 300-800 mg/ml of a crosslinking agent having a molecular weight in a range of about 5,000-15,000.

390. The method of claim ***382*** wherein -LM- is a diester diradical of the formula $-C(O)-(CH_2)_2-C(O)-$.

B1 Cont.

391. The method of claim ***382*** wherein -LM- is a diester diradical of the formula $-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated.

392. The method of claim **382** wherein -LM- is an oligomeric diradical derived from polyglycolic acid.

393. The method of claim ***364*** wherein the matrix binds tissue together in addition to a suture, a staple, a tape, or a bandage.

394. The method of claim ***364*** wherein the composition is provided to attach skin grafts.

395. The method of claim ***364*** wherein the composition is provided to attach adjacent layers of tissue.

396. The method of claim ***364*** wherein the composition is provided to position tissue flaps.

397. The method of claim ***364*** wherein the composition is provided to close gingival flaps.

398. A method of treating tissue comprising:

providing a composition to tissue, said composition including an albumin protein and a crosslinking agent ***at about 20-60 wt/vol%***, said crosslinking agent ***of about 50-800 mg/ml*** having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein ***and having a molecular weight in a range of about 1000-15,000***; and

curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix.

399. The method of claim ***398*** wherein said composition is cured to produce the matrix in less than about 10 minutes.

400. The method of claim ***398*** wherein said composition is cured to produce the matrix in less than about one minute.

B1 cont.

401. The method of claim ***398*** wherein said composition is cured to produce the matrix in about ten seconds.

402. The method of claim ***398*** comprising providing the composition to the tissue using a syringe.

403. The method of claim ***398*** comprising providing the composition to the tissue using a dual syringe.

404. The method of claim ***398*** comprising providing the composition to the tissue using a spray apparatus.

405. The method of claim ***398*** wherein the matrix is resorbed.

406. The method of claim ***405*** wherein the matrix is resorbed in about four to sixty days.

407. The method of claim ***398*** comprising curing the composition such that the peel strength of the matrix is about 0.08 lb/in or more.

408. The method of claim ***398*** comprising curing said composition to provide a cured matrix that has a burst pressure greater than about 10 mmHg.

409. The method of claim ***374*** wherein the matrix has a burst pressure of about 34 mmHg or greater.

410. The method of claim ***375*** wherein the matrix has a burst pressure of about 90 mmHg or greater.

411. The method of claim ***376*** wherein the matrix has a burst pressure of about 130 mmHg or greater.

412. The method of claim ***398*** comprising providing a composition wherein the crosslinking agent has a molecular weight in a range of about 1,000-5,000.

413. The method of claim ***398*** comprising providing a composition wherein the activated leaving group is an N-hydroxy imide.

414. The method of claim ***413*** comprising providing a composition wherein the activated leaving group is N-hydroxy succinimide.

415. The method of claim ***398*** further comprising mixing a first mixture and a second mixture to form the composition and applying said composition to the tissue,

wherein the first mixture includes about 20-60 wt/vol% of the protein in about 0.01-0.25 molar buffer at a pH in a range of about 8.0-11.0 and the second mixture includes about 50-800 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-15,000.

416. The method of claim ***415*** wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

$-O-(CH_2-CH_2-O-)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula, -C(O)-, a monoester diradical of the formula, $-(CH_2)_bC(O)-$

where b is an integer from 1-5, a diester radical of the formula, -C(O)-$(CH_2)_c$-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, and a dicarbonate diradical of the formula -C(O)-O-$(CH_2)_d$-O-C(O)- where d is an integer from 2-10, or an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-$(CH_2)_c$-C(O)-, or -R-C(O)-O-$(CH_2)_d$-O- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, or tresyl.

B1 Cont.

417. The method of claim ***416*** wherein the protein in the first mixture is about 35-45 wt/vol% serum albumin.

418. The method of claim ***417*** wherein the buffer is 0.05-0.15 molar carbonate/bicarbonate buffer at a pH of about 9.0-10.5.

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419. The method of claim ***416*** wherein the second mixture is about 5-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

420. The method of claim ***416*** wherein the ratio of a volume of the first mixture to a volume of the second mixture is in a range of about 1:10 to about 10:1.

421. The method of claim ***416*** wherein -LM- is an oligomeric diradical -R-C(O)-$(CH_2)_c$-C(O)- where c is an integer from 2-10 and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone.

422. The method of claim ***416*** wherein -G is succinimidyl.

423. The method of claim ***416*** wherein the second mixture includes about 300-800 mg/ml of a crosslinking agent having a molecular weight in a range of about 5,000-15,000.

424. The method of claim ***416*** wherein -LM- is a diester diradical of the formula $-C(O)-(CH_2)_2-C(O)-$.

425. The method of claim ***416*** wherein -LM- is a diester diradical of the formula $-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated.

426. The method of claim ***416*** wherein -LM- is an oligomeric diradical derived from polyglycolic acid.

427. The method of claim ***398*** comprising curing the composition on the tissue to seal the tissue.

428. The method of claim ***427*** comprising treating tissue to prevent or control a fluid leak.

429. The method of claim ***428*** wherein the fluid leak is a blood leak.

430. The method of claim ***427*** wherein the tissue includes an air leak.

431. The method of claim ***430*** wherein the air leak is in the pulmonary system.

432. The method of claim ***398*** wherein the composition is provided to tissue at a surgical site.

433. The method of claims ***398*** comprising curing the composition at the tissue to prevent a tissue adhesion.

434. The method of claim ***398*** wherein the composition is provided on a surface of an internal organ.

435. The method of claim ***398*** comprising curing the composition to form a matrix to bind tissue.

436. The method of claim ***435*** wherein the matrix binds tissue together in addition to a suture, a staple, a tape, or a bandage.

437. The method of claim ***398*** wherein the composition is provided to attach skin grafts.

438. The method of claim ***398*** wherein the composition is provided to attach adjacent layers of tissue.

439. The method of claim ***398*** wherein the composition is provided to position tissue flaps.

440. The method of claim ***398*** wherein the composition is provided to close gingival flaps.

B1 Conclude